Towards Validating Structural Connectivity in the Human Language System: An Intraoperative Cortico-Cortical Stimulation Experiment

Patryk Filipiak, Fabien Almairac, Théodore Papadopoulo, Denys Fontaine, Lydiane Mondot, Stéphane Chanalet, Maxime Descoteaux, Rachid Deriche, Maureen Clerc, Demian Wassermann

Towards Validating Structural Connectivity in the Human Language System: An Intraoperative Cortico-Cortical Stimulation Experiment

Patryk Filipiak[1], Fabien Almairac[2], Théodore Papadopoulo[1], Denys Fontaine[2], Lydiane Mondot[2], Stéphane Chanalet[2], Maxime Descoteaux[3], Rachid Deriche[1], Maureen Clerc[1], and Demian Wassermann[1,4]

[1] INRIA Sophia Antipolis-Méditerranée, Université Côte d'Azur, Valbonne, France
patryk.filipiak@inria.fr
[2] Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France,
[3] Sherbrooke Connectivity Imaging Lab (SCIL), University of Sherbrooke, Sherbrooke, QC, Canada
[4] INRIA, CEA, Université Paris-Saclay, Paris, France

Abstract. We aimed to validate structural connectivity measures based on diffusion MRI with Direct Electrical Stimulation (DES) of the human brain cortex. For this, we combined white matter fiber tractography with propagation of Cortico-Cortical Evoked Potentials (CCEPs) induced by intrasurgical DES in the language system of brain tumor patients. Our results showed high correlation (Pearson's coefficient 0.5-0.9) between delays of CCEPs and pathways connecting stimulation sites with recording electrodes. Our approach outperformed earlier study based on Diffusion Tensor Imaging. This potentially indicates that probabilistic tractography is an effective tool to quantify cortico-cortical communication non-invasively.

1 Introduction

We aimed to validate structural connectivity measures based on diffusion Magnetic Resonance Imaging (dMRI) with Direct Electrical Stimulation (DES) of the human brain cortex. For this, we combined probabilistic tractography with propagation of Cortico-Cortical Evoked Potentials (CCEPs) induced by intrasurgical DES in the language system of brain tumor patients. Our results showed high correlation (Pearson's coefficient 0.5-0.9) between delays of CCEPs and pathways connecting stimulation sites with recording electrodes. Despite the use of low-current 2.0-3.5 mA DES and a small-sized stimulating electrode, our findings were in accordance with the studies performed in different schemes [1–4], where higher current intensities and larger electrodes ensured better signal-to-noise ratio.

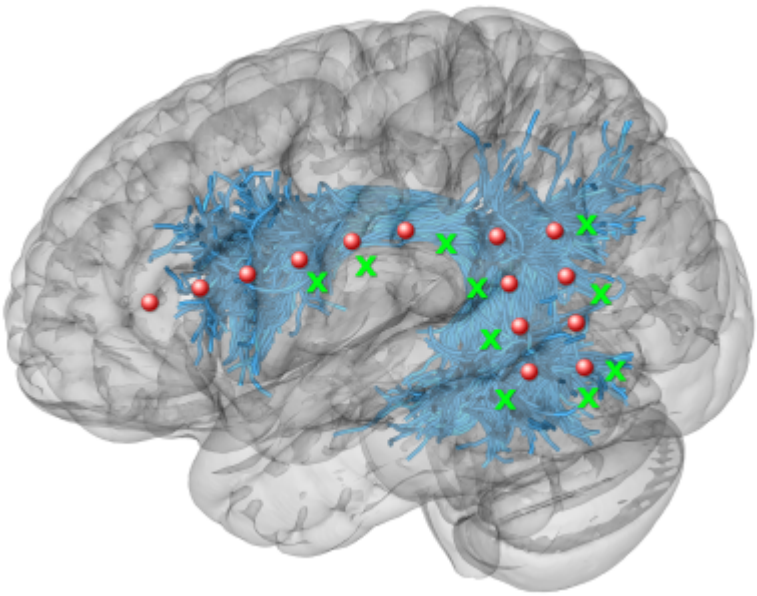

Fig. 1: Tractography-based Arcuate Fasciculus and Superior Longitudinal Fasciculus III (marked as blue streamlines), ECoG electrode placements (red circles), and stimulation points (green crosses).

2 Methods

We acquired pre-surgical multishell dMRI ($b \in \{400, 800, 1550, 3100\}$ [s/mm^2] with $\{6, 13, 29, 51\}$ directions, respectively), from which we obtained probabilistic tractography. We dissected Arcuate Fasciculus (AF) and Superior Longitudinal Fasciculus III (SLF3) with MI-Brain [5] to plan the positioning of recording electrocorticographic (ECoG) electrodes. Next, following the awake craniotomy procedure, a neurosurgeon performed brain cartography with high-frequency 50 Hz DES to identify functional cortical sites related to AF and SLF3. Then, we placed the ECoG electrodes on the cortical terminations of those tracts determined with structural information from the dMRI-based tractography and functional information from the DES-based cartography, as illustrated in Figure 1.

In this work, we considered two patients with written consent to participate in our study: 46-year old male (Patient 1) and 25-year old female (Patient 2). For both of them, we performed the ECoG recording under general anesthesia, right after the tumor resection. We used biphasic, bipolar 3.5 mA DES with the frequency 5 Hz for Patient 1 and 2.0 mA DES with the frequency 2 Hz for Patient 2. We recorded the signal, referenced to the average of all the electrodes, using the sampling frequency 2 kHz. The stimulation sites were located in the

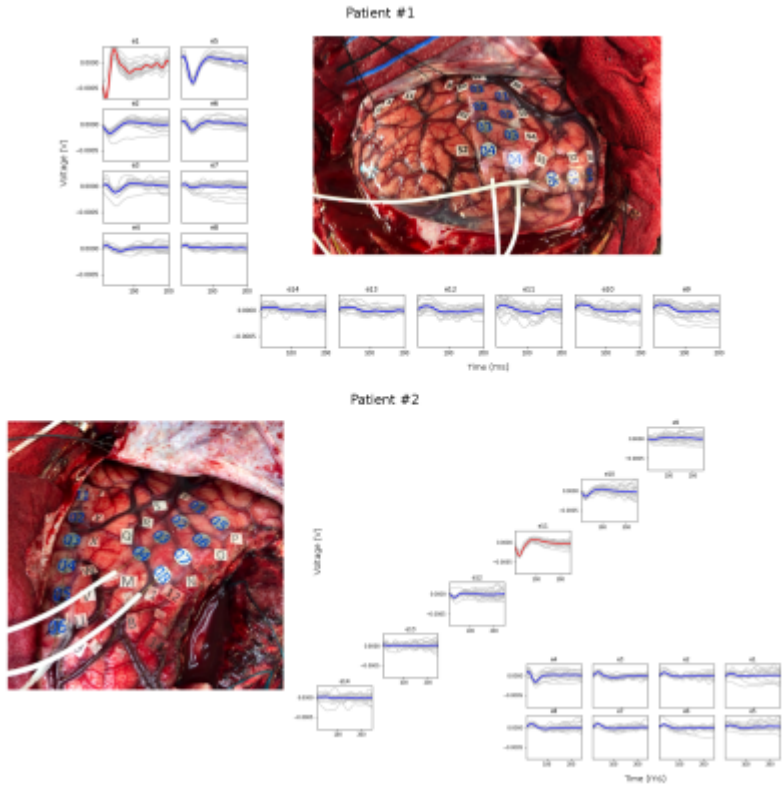

Fig. 2: Placement of ECoG electrodes and sample recordings of the CCEP propagation. The signals from the electrodes nearest the stimulation site are printed in red. The N1s are visible as downward peaks recorded by the electrodes located up to 4cm away from the stimulation site.

proximity of the reachable recording electrodes as illustrated in Figures 1 and 2. Each stimulation was repeated about 20 times.

In the post-processing, we averaged the ECoG signal of each DES trial in order to decrease the noise. Next, we computed the delays of the observed CCEPs and correlated them with the probability that a white matter bundle connects the stimulation and electrode sites. For that, we considered seeds located in the points of interest identified with the clinical neuronavigation system, surrounded by spheres of the 5 mm in diameter to account for a brain shift.

3 Results

Typically, an evoked potential consists of three consecutive voltage peaks named N1, P1, and N2 [6]. In most of our ECoG signals, we could identify the downward N1 peak propagating from the stimulation site, as illustrated in Figure 2.

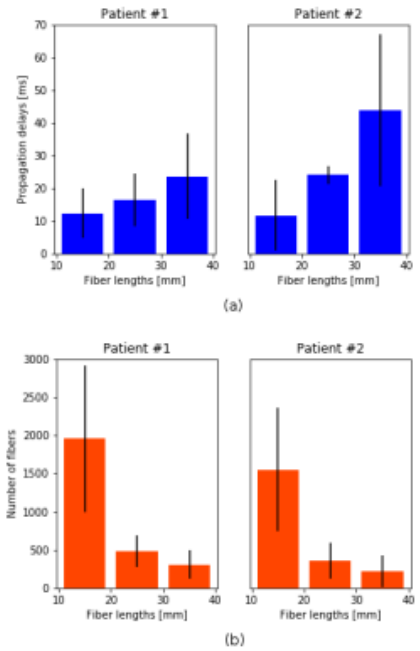

Fig. 3: Means and standard deviations of (a) CCEP delays, (b) number of fibers originating from a stimulation site. The measurements are aggregated by the fiber lengths. Our delays are in accordance with the literature.

Figure 3a illustrates the means and standard deviations of delays of the N1 peaks aggregated by the lengths of the shortest fibers connecting a given stimulation-recording pair. The results for Patient 1 are less dispersed, reaching 23.6±13.0 ms delay on the fibers between 30- and 40-millimeter long, while for the Patient 2 we observed 43.7±23.2 ms delay for the same distance length. Figure 3b summarizes the number of fibers linking the examined pairs of points aggregated by the lengths. As expected, the majority of fibers connect neighboring sites located 10-20 mm away from each other.

Figures 4 and 5 illustrate the correlation that we observed between delays of N1 and numbers of pathways connecting stimulation sites with recording electrodes. In most of the cases the Pearson's correlation coefficient laid between 0.5 and 0.9.

4 Discussion

Elucidating the relationship between structure and function of the brain is one of the main challenges in neuroscience [7]. In this work, we addressed an open question, whether tractography provides an index of cortico-cortical communication.

Fig. 4: Correlation between the probability that there is an axonal connection linking stimulation sites and recording electrodes, and the latencies of corresponding N1 peaks of the induced CCEPs for Patient 1. The Pearson's correlation coefficients and p-values are given for each stimulation site. Statistically significant results are printed in bold. The squares on white are the reference stimulation points.

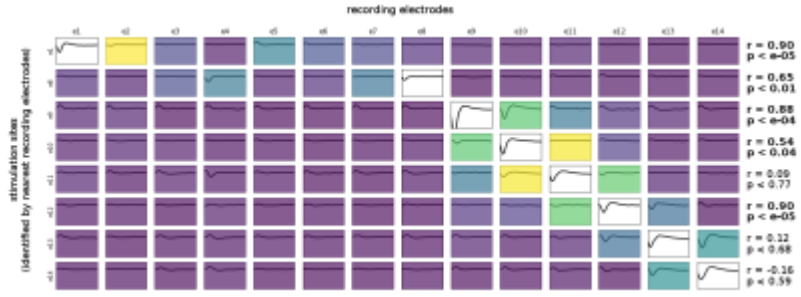

Fig. 5: Correlation between the probability that there is an axonal connection linking stimulation sites and recording electrodes, and the latencies of corresponding N1 peaks of the induced CCEPs for Patient 2. The Pearson's correlation coefficients and p-values are given for each stimulation site. Statistically significant results are printed in bold. The squares on white are the reference stimulation points.

We assesed the relationship between structural connectivity, measured through probabilistic tractography, and cortico-cortical communication as measured by injected DES. Despite being criticized, the correspondance between probabilistic tractography and the probability of an axonal connection has been accumulating positive evidence (e.g. in animal models [8]). In our case, the observed high correlation provides initial evidence that our tested hypothesis is correct. Our results outperform the previous streamline tractography study [2], where the Pearson's correlation coefficient 0.4 was reported for the pathways obtained from Diffusion Tensor Imaging. This potentially indicates that probabilistic tractography is an effective tool to quantify cortico-cortical communication non-invasively.

5 Conclusion

Our study validates the structural connectivity measures based on white matter tractography with the propagation of CCEPs. We believe that combining those two modalities will help understand the organization of cognitive functions and support neurosurgical planning.

Acknowledgements

This work has received funding from the ANR/NSF award NeuroRef; the MAXIMS grant funded by ICM's The Big Brain Theory Program and ANR-10-IAIHU-06.

References

1. Matsumoto, R., Nair, D.R., LaPresto, E., Najm, I., Bingaman, W., Shibasaki, H., Lüders, H.O.: Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain **127**(10) (2004) 2316–2330
2. Conner, C.R., Ellmore, T.M., DiSano, M.A., Pieters, T.A., Potter, A.W., Tandon, N.: Anatomic and electro-physiologic connectivity of the language system: a combined dti-ccep study. Computers in biology and medicine **41**(12) (2011) 1100–1109
3. Keller, C.J., Honey, C.J., Mégevand, P., Entz, L., Ulbert, I., Mehta, A.D.: Mapping human brain networks with cortico-cortical evoked potentials. Philosophical Transactions of the Royal Society B: Biological Sciences **369**(1653) (2014) 20130528
4. Yamao, Y., Matsumoto, R., Kunieda, T., Arakawa, Y., Kobayashi, K., Usami, K., Shibata, S., Kikuchi, T., Sawamoto, N., Mikuni, N., et al.: Intraoperative dorsal language network mapping by using single-pulse electrical stimulation. Human brain mapping **35**(9) (2014) 4345–4361
5. Imeka: Mi-brain website (2018)
6. Vincent, M., Guiraud, D., Duffau, H., Mandonnet, E., Bonnetblanc, F.: Electrophysiological brain mapping: Basics of recording evoked potentials induced by electrical stimulation and its physiological spreading in the human brain. (2017)
7. Jbabdi, S., Sotiropoulos, S.N., Haber, S.N., Van Essen, D.C., Behrens, T.E.: Measuring macroscopic brain connections in vivo. Nature neuroscience **18**(11) (2015) 1546

8. Donahue, C.J., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Behrens, T.E., Dyrby, T.B., Coalson, T., Kennedy, H., Knoblauch, K., Van Essen, D.C., et al.: Using diffusion tractography to predict cortical connection strength and distance: a quantitative comparison with tracers in the monkey. Journal of Neuroscience **36**(25) (2016) 6758–6770